Remarks

Reconsideration of this Application is respectfully requested.

Applicants submit that this amendment places the application in better condition for allowance or appeal. No new issues requiring further considerations or searching are raised. Accordingly, reconsideration of this application is respectfully requested.

Upon entry of the foregoing amendment, claims 1 and 4-17 are pending in the application, with claim 1 being the sole independent claim. The Examiner withdrew claims 6, 7 and 10-13 from consideration. Claims 2 and 3 have been canceled without prejudice or disclaimer of the subject matter therein, and claim 1 is sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 1-5, 8, 9 and 14-17 under 35 U.S.C. §103(a) as allegedly being obvious over Gowri *et al.* (AJH 1992; 12:744-766) and Gowri *et al.* (Am. J. Physiol. Endocrinol. Metab., 2000; 279:E593-E600) in view of Copp *et al.* (U.S. Pat. No. 4,572,913). (*See* Office Action at page 2). Applicants respectfully traverse the rejection.

1. The Examiner has not established a correlation between lipoxygenase activity and lowering of serum triglycerides.

The Examiner asserts that "Applicant in his remarks argues that the examiner has made the improper determination of masoprocol's status as a lipoxygenase inhibitor. However, applicant fails to establish that such a compound does not have lipoxygenase activity and the lowering of serum triglycerides and hypertension is not as a result of the inhibitory activity of the compound on the lipoxygenase pathway." (*See* Office Action at page 2). Contrary to the Examiner's assertion, the burden is not on the Applicant to show that masoprocol does not have lipoxygenase inhibitory activity; rather, the burden is on the Examiner to show that there is a correlation between 5-lipoxygenase inhibitory activity and the lowering of serum triglycerides. The Examiner must do this without relying on any teaching from the specification, as it is not proper to use information from Applicants' specification to establish a *prima facie* case of obviousness.

In order to prevent obviousness rejections based on hindsight analysis, the Federal Circuit has explained that even after *KSR* a flexible approach to the teaching-suggestion-motivation test remains the primary guarantor against the use of improper hindsight in establishing a rejection based on obviousness. *See Ortho-McNeil Pharmaceuticals, Inc. v Mylan Laboratories, Inc.* 520 F.3d 1358, at 1364 and 1365 (Fed. Cir. 2008). It is recognized that the teaching, suggestion or motivation need not always be found in the writing but may be found within the knowledge and creativity of the ordinary artisan. *Id.* at 1365. Applicants assert that without looking at the present specification there would be no reason to think that a phenyl pyrazoline derivative will be effective at lowering serum triglyceride levels. This is especially true since it was known at the time the invention was made that classification as a 5-lipoxygenase

inhibitor was not necessarily predictive of a lowering serum triglyceride effect. For example, esculetin is a 5-lipoxygenase inhibitor that does not lower serum triglyceride levels. *See* Gowri. *et al.* (Am. J. Physiol. Endocrinol. Metab., at p. E599, col. 2, ll. 4-5) (hereinafter "Gowri 2000"). Thus, a serum triglyceride lowering effect is not predictably associated with 5-lipoxygenase activity.

The Examiner further alleges that "in view of the prior art and based on KSR a person skilled in the art would have been motivated to try and use a compound having lipoxygenase activity inhibitory activity for the treatment of elevated serum triglycerides or hypertention." (Office Action at page 2). Applicants respectfully disagree with this position.

The present application is drawn to a method of treating elevated serum triglyceride levels by the administration of a pharmaceutical composition comprising a 5-lipoxygenase inhibitor. The enzyme 5-lipoxygenase converts arachidonic acid to 5-hyrdoxyperoxyeicosatetraenoic acid (5-HPETE). There is no indication in the art, or based on the general knowledge of the ordinary artisan, that the 5-lipoxygenase enzyme is involved in the synthesis of triglycerides. The 5-lipoxygenase enzyme also does not play a role in release or absorption of triglycerides in and out of the blood stream into tissues where the fatty acids may be stored or used for energy. (*See* attached Exhibit A, Pulliger, C.R. and Kane, J.P. "Lipid metabolism and transport," in *Molecular Biology and Biotechnology*, Meyers R.A. ed., VCH Publishers New York, pp.494-501 (1995), specifically figures 1 and 2.) Thus, the ordinary artisan would *not* have reasonably looked to administer a 5-lipoxygenase inhibitor in order to lower triglyceride levels in the serum of a patient.

In addition, the Examiner has not established that it is the 5-lipoxygenase inhibitory activity of masoprocol that is responsible for the antilipolytic effect in the treated subject. The two references cited by the Examiner disclose using masoprocol *in vivo*, and both observe that masoprocol has antilipolytic activity associated with the compound. However, antilipolytic activity is not the only activity associated with masoprocol, as masoprocol possesses many physiological activities including lipoxygenase inhibition, antioxidant activity, and dephosphorylating hormone sensitive lipase [HSL]. *See* Gowri 2000, at E593. Thus, the references do not establish that it is the 5-lipoxygenase inhibitory activity that causes the lowering of the serum triglyceride levels.

In particular, in Gowri 2000 it is asserted that "[t]he antilipolytic activity effect of masoprocol on isolated adipocytes was associated with a fall in HSL [hormone sensitive lipase] activity, and by using an anti phosphoserine antibody, we were able to show that this loss in activity was associated with a decrease in the phosphorylated state of HSL. This confirms that masoprocol may be stimulating a serine/threonine phosphatase via a second messenger pathway and may be causing dephosphorylation of HSL." Gowri 2000 at E593. The phosphorylated form of hormone sensitive lipase is the active form, and the active form converts the cellular triglyceride stored in adipocytes into free fatty acids and glycerol. The antilipolytic activity may be associated with an interaction between the inhibitor and hormone sensitive lipase and not between the inhibitor and 5-lipoxygenase. In fact, in view of masoprocol's numerous physiological activities, it is likely that the serum lowering effect of masoprocol is due to the dephosphorylation of HSL and not the effect on lipoxygenase. Thus, the correlation between the 5-

lipoxygenase inhibitory activity and the serum triglyceride lowering activity has not been established. Without this correlation the ordinary artisan could not reasonably predict that a 5-lipoxygenase inhibitor would be effective at lowering serum triglyceride levels.

Accordingly, for at least the reasons set out above, Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness by showing a correlation between 5-lipoxygenase activity and serum triglyceride lowering effect.

2. Masoprocol as the lead compound would not direct the ordinary artisan to a phenyl pyrazoline derivative as a compound for triglyceride lowering activity.

A *prima facie* case obviousness involving structurally similar compounds requires a showing that there is adequate support in the prior art for the changing of the structure of a compound. *See Takeda Chemical Industries v. Alphapharm*, 492 F.3d 1350, at 1356 (2007), citing *In re Grabiak*, 769 F.2d 729, at 731-732 (Fed. Cir. 1985). "Normally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." *Takeda* 492 F.3d at 1356 citing *In re Deuel*, 51 F.3d 1552, at 1558 (Fed. Cir. 1995). There is the additional requirement that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Id.* citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984). The court held that in "cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound." *Takeda*, 492 F.3d at 1357. Thus, the holding in *Takeda*

provides that a *prima facie* case of obviousness requires the identification of a lead compound in the references followed by a clear articulation of the reasons why the artisan would change the compound in a particular way to achieve a predictable result.

Here, the cited compounds are not structurally similar. *See* Exhibit B. Even assuming, *arguendo*, the ordinary artisan would choose masoprocol or curcumin as the lead compound, there is nothing in the art that would lead the ordinary artisan to modify either compound in such a way that the ordinary artisan would arrive at the phenyl pyrazoline derivative structure.

Furthermore, neither Gowri reference shows that lipoxygenase inhibitors, acting through the 5-lipoxygenase pathway, act to lower serum triglycerides. The speculative nature of both Gowri references in linking the lipoxygenase pathway to masoprocol's observed effects and the observation of another (non-phenyl pyrazoline derivative) lipoxygenase inhibitor (esculetin) not having the same antilipolytic properties that masoprocol has would certainly not rise to the level of providing predictability and motivating one skilled in the art to substitute one lipoxygenase inhibitor for another lipoxygenase, especially in view of the divergent structures.

Accordingly, for at least the reasons set out above, Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness based on changing the structure of the lead chemical compound to arrive at a phenyl pyrazoline derivative. Thus, there is no reason for the ordinary artisan to choose phenyl pyrazoline derivative in methods of lowering serum triglyceride levels.

3. The previously presented arguments articulated in the Reply filed April 8, 2008, are referenced herein in their entirety.

The arguments submitted in the Reply of April 8, 2008, are referenced herein in their entirety. In summary, the arguments were as follows: (a) that the Examiner did not articulate with particularity the reasons to support the finding that one skilled in the art would have substituted one element for another, as such the Examiner merely presented a conclusory statement without providing any evidence that masoprocol only acts as a lipoxygenase inhibitor and has *no* other physiological effects contrary to the teaching in Gowri 2000; (b) a person of ordinary skill in the art would not have found the claimed invention predictable, especially in view of the observation that not all lipoxygenase inhibitors have antilipolytic activity; and (c) there is no reasonable expectation of success in combining the Gowri references with Copp to arrive at the claimed invention, since the two Gowri references had mixed success with lipoxygenase inhibitors tested therby discouraging the ordinary artisan from combing the references directed to different types of lipoxygenase inhibitors.

For at least the reasons set out above in conjunction with the reasons set out in the reply of April 8, 2008, the scope and content of the art would not have allowed a person of ordinary skill in the art to *predictably* arrive at the claimed invention, as required under *KSR* and the USPTO Examination Guidelines. Therefore, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness and respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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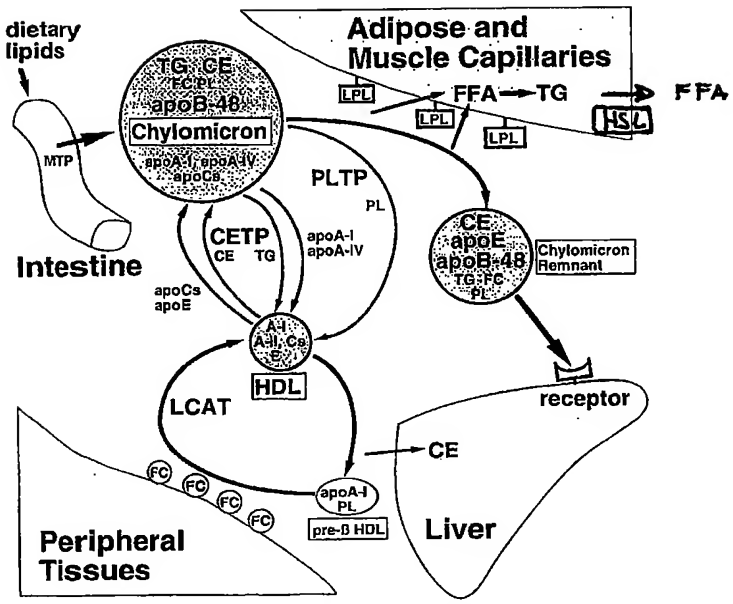


Figure 1. Exogenous lipid transport: FC, free cholesterol; CE, cholesteryl ester; PL, phospholipid; TG, triglyceride; FFA, free fatty acid; LPL, lipoprotein lipase; LCAT, lecithin–cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; PLTP, phospholipid transfer protein; MTP, microsomal triglyceride transfer protein.

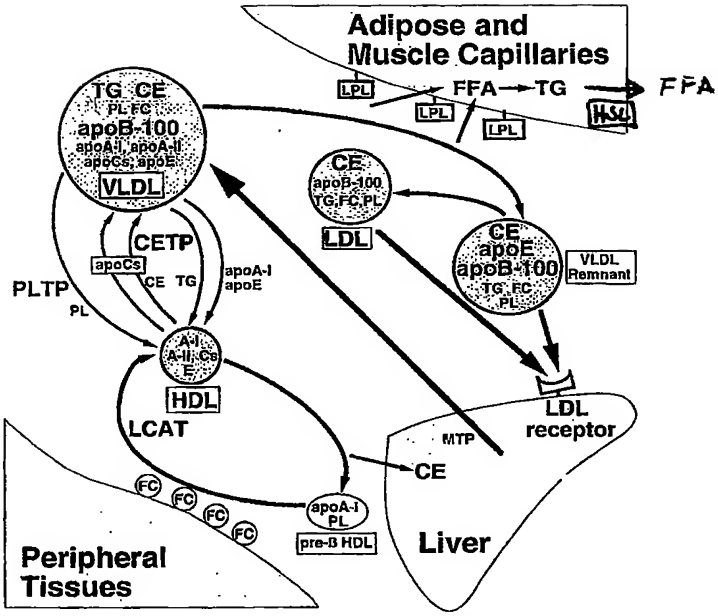
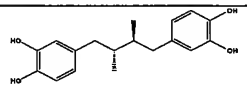
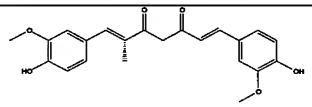
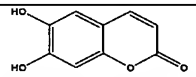
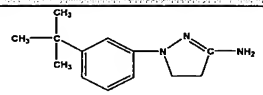
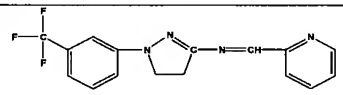
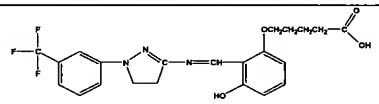
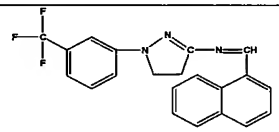
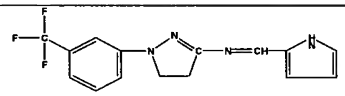
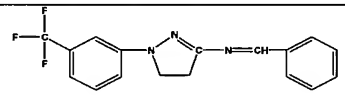
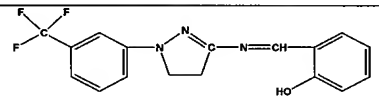
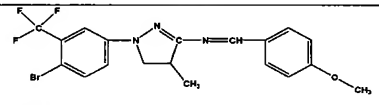
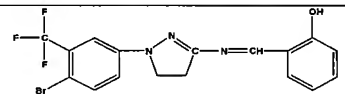
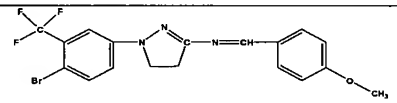
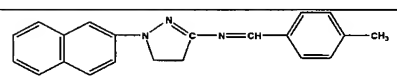


Figure 2. Endogenous lipid transport: FC, free cholesterol; CE, cholesteryl ester; PL, phospholipid; TG, triglyceride; FFA, free fatty acid; LPL, lipoprotein lipase; LCAT, lecithin–cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; PLTP, phospholipid transfer protein; MTP, microsomal triglyceride transfer protein.

Structure Comparison of Lipoxygenase Inhibitors — Exhibit B

Compound	Structure	Lipoxygenase inhibitory activity	Triglyceride lowering
Masoprocol, nordihydroguiaiaretic acid (NDGA) Triglyceride lowering effect is excreted through the hormone sensitive lipase inactivation (*see* specification [0004])		**YES**	**YES**
Curcumin The molecular aspects of the triglyceride lowering activity have not been determined (*see* specification [0006])		**YES**	**YES**
Esculetin (Gowri *et al.*, 2000)		**YES**	**NO**
4,5,dihydro-1-(3-trifluoromethylphenyl)-1H-pyrazol-3-amine (*see* specification table 2)		**YES**	**YES**
3-Amino-1-(3-t-butylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = <1$	ND
3-(2-pyridylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = \sim 3$	ND
3-(2,4'-carboxybutoxy-6-hydroxybenzylidine-amino)-1-(3-trifluoromethylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = 10\text{-}20$	ND
3-(1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = 6$	ND
3-(2-pyrrolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = 1$	ND
3-Benzylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline		$IC_{50}(\mu M) = <1$	ND
3-salicylidenamino-1-(3-trifluoromethylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = \sim 3$	ND
4-Methyl-3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) \sim 1$	ND
1-(4-bromo-3-trifluoromethylphenyl)-3-(2-hydroxybenzylideneamino)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = >10$	ND
1-(4-bromo-3-trifluoromethylphenyl)-3-(4-methoxybenzylideneamino)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = \sim 1$	ND
3-(4-methylbenzylideneamino)-1-(2-naphthyl)-2-pyrazoline (US 4,572,912)		$IC_{50}(\mu M) = 12$	ND